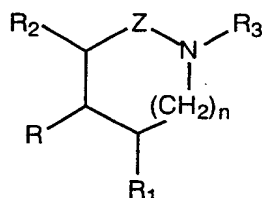


What is claimed is:

1. A compound of the formula:

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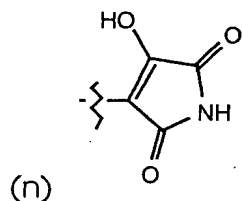


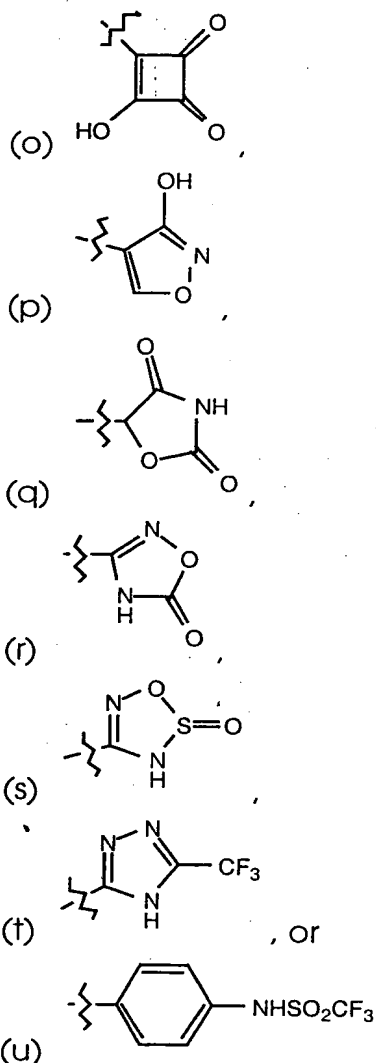
wherein

- 10 Z is $-C(R_{18})(R_{19})-$ or $-C(O)-$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;
n is 0 or 1;

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

- 15 (a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,
(b) $-PO_3H_2$,
(c) $-P(O)(OH)E$ wherein E is hydrogen, loweralkyl or arylalkyl,
(d) $-CN$,
(e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,
(f) alkylaminocarbonyl,
20 (g) dialkylaminocarbonyl,
(h) tetrazolyl,
(i) hydroxy,
(j) alkoxy,
(k) sulfonamido,
25 (l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,
(m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,





- R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;
- R_3 is (a) $R_4-C(O)-R_5$, R_4-R_5a , $R_4-C(O)-R_5-N(R_6)$, $R_6-S(O)_2-R_7$ or $R_{26}-S(O)-R_{27}$ wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) $-N(R_{20})-R_8$ or $-R_{8a}-N(R_{20})-R_8$

wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v) $-O-R_9-$ or $-R_{9a}-O-R_9-$ wherein R_9 and R_{9a} are independently selected from alkylene;

5 R_{5a} is (i) alkylene or (ii) alkenylene;

R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{21})-R_{10}-$ or $-R_{10a}-N(R_{21})-R_{10}-$ wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

10 R_4 and R_6 are independently selected from the group consisting of

(i) $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl,
- 15 (4) alkoxyalkyl,
- (5) haloalkoxyalkyl,
- (6) alkenyl,
- (7) alkynyl,
- (8) cycloalkyl,
- 20 (9) cycloalkylalkyl,
- (10) aryl,
- (11) heterocyclic,
- (12) arylalkyl,
- (13) (heterocyclic)alkyl,
- 25 (14) hydroxyalkyl,
- (15) alkoxy,
- (16) aminoalkyl,
- (17) trialkylaminoalkyl,
- (18) alkylaminoalkyl,
- 30 (19) dialkylaminoalkyl, and
- (20) carboxyalkyl

(ii) loweralkyl,

(iii) alkenyl,

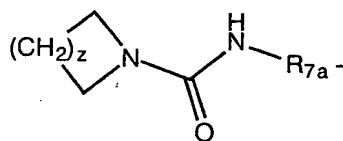
(iv) alkynyl,

35 (v) cycloalkyl,

(vi) cycloalkylalkyl,

(vii) aryl,

- (viii) arylalkyl,
 (ix) heterocyclic,
 (x) (heterocyclic)alkyl,
 (xi) alkoxyalkyl,
 5 (xii) hydroxyalkyl,
 (xiii) haloalkyl,
 (xiv) haloalkenyl,
 (xv) haloalkoxyalkyl,
 (xvi) haloalkoxy,
 10 (xvii) alkoxyhaloalkyl,
 (xviii) alkylaminoalkyl,
 (xix) dialkylaminoalkyl,
 (xx) alkoxy, and



- 15 (xxi)
 wherein z is 0-5 and R_{7a} is alkylene;

R₂₆ is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and
 20 R₂₇ is alkylene or alkenylene;

- (b) R₂₂-O-C(O)-R₂₃- wherein R₂₂ is a carboxy protecting group or heterocyclic and R₂₃ is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) -N(R₂₄)-R₂₅- wherein R₂₅ is alkylene and R₂₄ is hydrogen or loweralkyl,
 25 (c) loweralkyl,
 (d) alkenyl,
 (e) alkynyl,
 (f) cycloalkyl,
 (g) cycloalkylalkyl,
 30 (h) aryl,
 (i) arylalkyl,
 (j) aryloxyalkyl,
 (k) heterocyclic,
 (l) (heterocyclic)alkyl,
 35 (m) alkoxyalkyl,

(n) alkoxyalkoxyalkyl, or

(o) $R_{13}-C(O)-CH(R_{14})-$

wherein R_{13} is amino, alkylamino or dialkylamino and R_{14} is aryl or $R_{15}-C(O)-$

wherein R_{15} is amino, alkylamino or dialkylamino;

5 or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 wherein n is 0 and Z is $-CH_2-$.

10 3. The compound according to Claim 1 wherein n is 1 and Z is $-CH_2-$.

4. The compound according to Claim 1 wherein n is 0, Z is $-CH_2-$,
and R_3 is $R_4-C(O)-R_5-$, $R_6-SO_2-R_7-$ or $R_{26}-S(O)-R_{27}-$ wherein R_4 , R_5 , R_6 , R_7 , R_{26}
15 and R_{27} are as defined therein.

5. The compound according to Claim 1 wherein n is 0, Z is $-CH_2-$,
and R_3 is alkoxyalkyl or alkoxyalkoxyalkyl.

20 6. The compound according to Claim 1 wherein n is 0, Z is $-CH_2-$,
and R_3 is $R_4-C(O)-R_5-$ wherein R_4 is $(R_{11})(R_{12})N-$ as defined therein and R_5 is
alkylene or R_3 is $R_6-S(O)_2-R_7-$ or $R_{26}-S(O)-R_{27}-$ wherein R_7 is alkylene, R_{27} is
alkylene and R_6 and R_{26} are as defined therein.

25 7. The compound according to Claim 1 wherein n is 0, Z is $-CH_2-$
and R_3 is $R_4-C(O)-N(R_{20})-R_8-$ or $R_6-S(O)_2-N(R_{21})-R_{10}-$ wherein R_8 and R_{10} are
alkylene and R_4 , R_6 , R_{20} and R_{21} are as defined therein.

30 8. The compound according to Claim 1 wherein n is 0, R is tetrazolyl
or $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group or R is
tetrazolyl or R is $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z
is $-CH_2-$, R_1 and R_2 are independently selected from (i) loweralkyl, (ii)
cycloalkyl, (iii) substituted and unsubstituted aryl wherein aryl is phenyl
substituted with one, two or three substituents independently selected from
35 loweralkyl, alkoxy, halo, alkoxyalkoxy and carboxyalkoxy, (iv) substituted or
unsubstituted heterocyclic, (v) alkenyl, (vi) heterocyclic (alkyl), (vii)
aryloxyalkyl, (viii) arylalkyl, (ix) (N-alkanoyl-N-alkyl)aminoalkyl, and (x)

alkylsulfonylamidoalkyl, and R_3 is $R_4-C(O)-R_5$ - wherein R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, aryl and arylalkyl and R_5 is alkylene; or R_3 is

- 5 $R_4-C(O)-N(R_{20})-R_8$ - or $R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein R_4 is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and R_6 is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl, R_8 and R_{10} are alkylene and R_{20} and R_{21} are loweralkyl; or R_3 is $R_6-S(O)_2-R_7$ - or $R_{26}-S(O)-R_{27}$ - wherein R_6 is loweralkyl or haloalkyl, R_7 is alkylene, R_{26} is loweralkyl and R_{27} is alkylene.

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9. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, 15 (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or 20 dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, 25 dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl, or difluorophenyl, and R_3 is $R_4-C(O)-N(R_{20})-R_8$ - or $R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein R_8 and R_{10} are alkylene, R_{20} and R_{21} are loweralkyl, R_4 is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and R_6 is loweralkyl, haloalkyl, alkoxyalkyl, aryl or arylalkyl.

30

10. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, 35 (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl,

3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl or (xiii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl, or difluorophenyl, and R_3 is $R_4-C(O)-R_5$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl, arylalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, and trialkylaminoalkyl.

11. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i) loweralkyl (ii) alkenyl, (iii) arylalkyl, (iv) aryloxyalkyl, (v) heterocyclic, (vi) heterocyclic (alkyl), (vii) aryl, (viii) (N-alkanoyl-N-alkyl)aminoalkyl, or (viii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is $R_4-C(O)-R_5$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} is loweralkyl, and R_{12} is aryl or arylalkyl.

12. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i) phenyl or (ii) substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy, and carboxyalkoxy, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is

$R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl and R_{21} is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl.

- 5 13. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl or 1,4-benzodioxanyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy and alkoxyalkoxy, R_2 is substituted or
- 10 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the
- 15 substituent is selected from loweralkyl, alkoxy and halogen and R_3 is alkoxycarbonyl or $R_6-S(O)_2-N(R_{21})-R_{10}$ - wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{21} is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.
- 20 14. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, Z is $-CH_2-$, R_1 is substituted or
- 25 unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5$ -
- 30 wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.
- 35 15. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$

wherein R_{16} is loweralkyl or haloalkyl, Z is $-CH_2-$, R_1 is loweralkyl, alkoxyalkyl, or alkenyl, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$

- 5 wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from loweralkyl, aryl hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, heterocyclic, and arylalkyl.

- 10 16. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from loweralkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, aryl, and heterocyclic.

17. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} is loweralkyl and R_{12} is aryl.

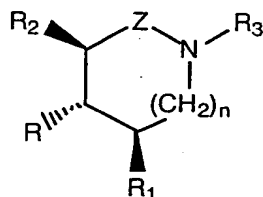
- 35 18. The compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-

- fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is substituted or
- 5 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is $R_4-C(O)-R_5$ - wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} is alkyl
- 10 and R_{12} is selected from aryl, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

19. A compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and R_3 is $R_4-C(O)-R_5$ - wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

20. A compound according to Claim 1 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and R_3 is $R_4-C(O)-R_5$ - wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic, with the proviso that one or R_{11} and R_{12} is alkyl.

21. The compound according to Claim 1 of the formula:



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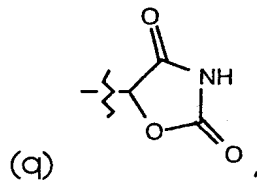
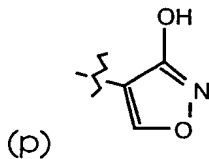
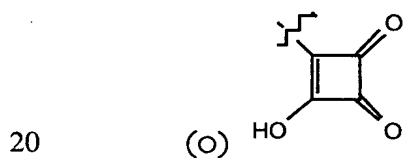
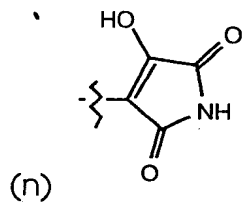
wherein

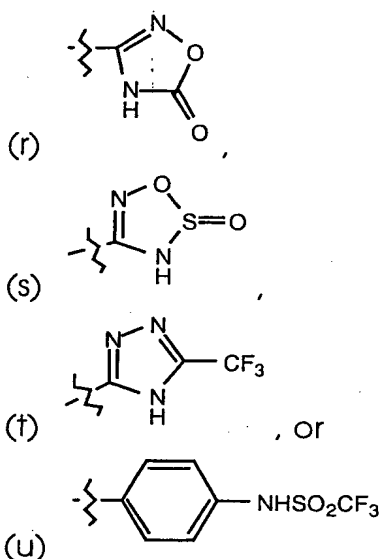
Z is $-C(R_{18})(R_{19})-$ or $-C(O)-$ wherein R_{18} and R_{19} are independently selected from hydrogen and loweralkyl;

n is 0 or 1;

R is $-(CH_2)_m-W$ wherein m is an integer from 0 to 6 and W is

- 5 (a) $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group,
- (b) $-PO_3H_2$,
- (c) $-P(O)(OH)E$ wherein E is hydrogen, loweralkyl or arylalkyl,
- (d) $-CN$,
- (e) $-C(O)NHR_{17}$ wherein R_{17} is loweralkyl,
- 10 (f) alkylaminocarbonyl,
- (g) dialkylaminocarbonyl,
- (h) tetrazolyl,
- (i) hydroxy,
- (j) alkoxy,
- 15 (k) sulfonamido,
- (l) $-C(O)NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl, aryl or dialkylamino,
- (m) $-S(O)_2NHC(O)R_{16}$ wherein R_{16} is defined as above,





- 5 R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl,
- 10 alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ - wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than
- 15 hydrogen;
- R_3 is (a) $R_4-C(O)-R_5$ -, R_4-R_{5a} -, $R_6-S(O)_2-R_7$ - or $R_{26}-S(O)-R_{27}$ - wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) $-N(R_{20})-R_8$ - or $-R_{8a}-N(R_{20})-R_8$ - wherein R_8 and R_{8a} are independently selected from the group consisting of
- 20 alkylene and alkenylene and R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v) $-O-R_9$ - or $-R_{9a}-O-R_9$ - wherein R_9 and R_{9a} are independently selected from alkylene;
- R_{5a} is (i) alkylene or (ii) alkenylene;
- 25 R_7 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{21})-R_{10}$ - or $-R_{10a}-N(R_{21})-R_{10}$ -

wherein R_{10} and R_{10a} are independently selected from the group consisting of alkylene and alkenylene and R_{21} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

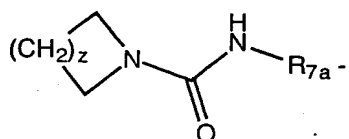
R_4 and R_6 are independently selected from the group consisting of

5 (i) $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from

- (1) hydrogen,
- (2) loweralkyl,
- (3) haloalkyl,
- 10 (4) alkoxyalkyl,
- (5) haloalkoxyalkyl,
- (6) alkenyl,
- (7) alkynyl,
- (8) cycloalkyl,
- 15 (9) cycloalkylalkyl,
- (10) aryl,
- (11) heterocyclic,
- (12) arylalkyl,
- (13) (heterocyclic)alkyl,
- 20 (14) hydroxyalkyl,
- (15) alkoxy,
- (16) aminoalkyl, and
- (17) trialkylaminoalkyl,

- (ii) loweralkyl,
- 25 (iii) alkenyl,
- (iv) alkynyl,
- (v) cycloalkyl,
- (vi) cycloalkylalkyl,
- (vii) aryl,
- 30 (viii) arylalkyl,
- (ix) heterocyclic,
- (x) (heterocyclic)alkyl,
- (xi) alkoxyalkyl,
- (xii) hydroxyalkyl,
- 35 (xiii) haloalkyl,
- (xiv) haloalkenyl,
- (xv) haloalkoxyalkyl,

- (xvi) haloalkoxy,
 (xvii) alkoxyhaloalkyl,
 (xviii) alkylaminoalkyl,
 (xix) dialkylaminoalkyl,
 5 (xx) alkoxy, and



wherein z is 0-5 and R_{7a} is alkylene;

- 10 R_{26} is (i) loweralkyl, (ii) haloalkyl, (iii) alkenyl, (iv) alkynyl, (v) cycloalkyl, (vi) cycloalkylalkyl, (vii) aryl, (viii) arylalkyl, (ix) heterocyclic, (x) (heterocyclic)alkyl, (xi) alkoxyalkyl or (xii) alkoxy-substituted haloalkyl; and R_{27} is alkylene or alkenylene;

- 15 (b) $R_{22}-O-C(O)-R_{23}-$ wherein R_{22} is a carboxy protecting group or heterocyclic and R_{23} is (i) a covalent bond, (ii) alkylene, (iii) alkenylene or (iv) $-N(R_{24})-R_{25}-$ wherein R_{25} is alkylene and R_{24} is hydrogen or loweralkyl,

- (c) loweralkyl,
 (d) alkenyl,
 20 (e) alkynyl,
 (f) cycloalkyl,
 (g) cycloalkylalkyl,
 (h) aryl,
 (i) arylalkyl,
 25 (j) aryloxyalkyl,
 (k) heterocyclic,
 (l) (heterocyclic)alkyl,
 (m) alkoxyalkyl,
 (n) alkoxyalkoxyalkyl, or
 30 (o) $R_{13}-C(O)-CH(R_{14})-$

wherein R_{13} is amino, alkylamino or dialkylamino and R_{14} is aryl or $R_{15}-C(O)-$ wherein R_{15} is amino, alkylamino or dialkylamino;

or a pharmaceutically acceptable salt thereof.

22. The compound according to Claim 21 wherein n is 0 and Z is -CH₂-.

5 23. The compound according to Claim 21 wherein n is 1 and Z is -CH₂-.

24. The compound according to Claim 21 wherein n is 0, Z is -CH₂-, and R₃ is R₄-C(O)-R₅-, R₆-SO₂-R₇- or R₂₆-S(O)-R₂₇- wherein R₄, R₅, R₆, R₇, R₂₆ and R₂₇ are as defined therein.

25. The compound according to Claim 21 wherein n is 0, Z is -CH₂-, and R₃ is alkoxyalkyl or alkoxyalkoxyalkyl.

15 26. The compound according to Claim 21 wherein n is 0, Z is -CH₂-, and R₃ is R₄-C(O)-R₅- wherein R₄ is (R₁₁)(R₁₂)N- as defined therein and R₅ is alkylene or R₃ is R₆-S(O)₂-R₇- or R₂₆-S(O)-R₂₇- wherein R₇ is alkylene, R₂₇ is alkylene and R₆ and R₂₆ are as defined therein.

20 27. The compound according to Claim 21 wherein n is 0, Z is -CH₂- and R₃ is R₄-C(O)-N(R₂₀)-R₈- or R₆-S(O)₂-N(R₂₁)-R₁₀- wherein R₈ and R₁₀ are alkylene and R₄, R₆, R₂₀ and R₂₁ are as defined therein.

28. The compound according to Claim 21 wherein n is 0, R is
25 tetrazolyl or -C(O)₂-G wherein G is hydrogen or a carboxy protecting group or R is tetrazolyl or R is -C(O)-NHS(O)₂R₁₆ wherein R₁₆ is loweralkyl, haloalkyl or aryl, Z is -CH₂-, R₁ and R₂ are independently selected from (i) loweralkyl, (ii) cycloalkyl, (iii) substituted and unsubstituted aryl wherein aryl is phenyl substituted with one, two or three substituents independently selected from
30 loweralkyl, alkoxy, halo, alkoxyalkoxy and carboxyalkoxy and (iv) substituted or unsubstituted heterocyclic, (v) alkenyl, (vi) heterocyclic (alkyl), (vii) aryloxyalkyl, (viii) aryalkyl, (ix) (N-alkanoyl-N-alkyl)aminoalkyl, and (x) alkylsulfonylamidoalkyl, and R₃ is R₄-C(O)-R₅- wherein R₄ is (R₁₁)(R₁₂)N- wherein R₁₁ and R₁₂ are independently selected
35 from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, aryl and arylalkyl and R₅ is alkylene; or

R_3 is $R_4-C(O)-N(R_{20})-R_8-$ or $R_6-S(O)_2-N(R_{21})-R_{10}-$
wherein R_4 is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and
 R_6 is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl,
 R_8 and R_{10} are alkylene and R_{20} and R_{21} are loweralkyl; or

- 5 R_3 is $R_6-S(O)_2-R_7-$ or $R_{26}-S(O)-R_{27}-$
wherein R_6 is loweralkyl or haloalkyl,
 R_7 is alkylene,
 R_{26} is loweralkyl and
 R_{27} is alkylene.

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29. The compound according to Claim 21 wherein n is 0, R is
 $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or
 $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i)
loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl,
15 (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-
fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl,
4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl,
3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-
hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or
20 dihydrobenzofuranyl wherein the substituent is selected from alkoxy,
alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic
(alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, R_2 is
substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl,
1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl,
25 benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or
difluorophenyl and R_3 is $R_4-C(O)-N(R_{20})-R_8-$ or $R_6-S(O)_2-N(R_{21})-R_{10}-$
wherein R_8 and R_{10} are alkylene,
 R_{20} and R_{21} are loweralkyl,
 R_4 is loweralkyl, aryl, alkoxy, alkylamino, aryloxy or arylalkoxy and
30 R_6 is loweralkyl, haloalkyl, alkoxyalkyl, aryl or arylalkyl.

30. The compound according to Claim 21 wherein n is 0, R is
 $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or
 $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i)
35 loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl,
(vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-
fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl,

4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy,

- 5 alkoxyalkoxy and carboxyalkoxy, (ix) aryalkyl, (x) aryoxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or
10 difluorophenyl and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl, heterocyclic, hydroxyalkyl, alkoxy, aminoalkyl, and trialkylaminoalkyl.

- 15 31. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i) loweralkyl or (ii) alkenyl, (iii) aryalkyl, (iv) aryoxyalkyl, (v) heterocyclic (alkyl), (vi) aryl, (vii) (N-alkanoyl-N-alkyl)aminoalkyl, or (viii) alkylsulfonylamidoalkyl, R_2
20 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is $R_4-C(O)-R_5-$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$
25 wherein R_{11} is loweralkyl and R_{12} is aryl or arylalkyl.

32. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is (i)
30 phenyl or (ii) substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is substituted or
35 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the

substituent is selected from loweralkyl, alkoxy and halogen and R_3 is $R_6-S(O)_2-N(R_{21})-R_{10}$ wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl and R_{21} is loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl.

5

33 The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl, haloalkyl or aryl, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl or 1,4-benzodioxanyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy and alkoxyalkoxy, R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is alkoxy carbonyl or $R_6-S(O)_2-N(R_{21})-R_{10}$ wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{21} is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl.

20

34. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from loweralkyl, aryl arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

35

35. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, tetrazolyl or $-C(O)-NHS(O)_2R_{16}$ wherein R_{16} is loweralkyl or haloalkyl, Z is $-CH_2-$, R_1 is

loweralkyl, alkoxyalkyl or alkenyl, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5$ - wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from
 5 loweralkyl, aryl, arylalkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic.

36. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1
 10 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and
 15 carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5$ - wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from loweralkyl.

20
 37. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 2-fluorophenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-
 25 pentafluoroethylphenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-ethylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is 1,3-benzodioxolyl, 1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl,
 30 fluorophenyl or difluorophenyl and R_3 is $R_4-C(O)-R_5$ - wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} is loweralkyl and R_{12} is aryl.

38. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1
 35 is substituted or unsubstituted 4-methoxyphenyl, 3-fluoro-4-methoxyphenyl, 3-fluorophenyl, 2-fluorophenyl, 3-fluoro-4-ethoxyphenyl, 4-methoxymethoxyphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or

dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, R_2 is substituted or

unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, 4-

- 5 methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen and R_3 is $R_6-S(O)_2-N(R_{21})-R_{10}$ wherein R_{10} is alkylene, R_6 is loweralkyl, haloalkyl, alkoxyalkyl or haloalkoxyalkyl and R_{21} is loweralkyl, haloalkyl or alkoxyalkyl.

- 10 39. The compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and R_3 is $R_4-C(O)-R_5$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are
15 independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, and heterocyclic.

40. A compound according to Claim 21 wherein n is 0, R is $-C(O)_2-G$ wherein G is hydrogen or a carboxy protecting group, Z is $-CH_2-$, R_1 is
20 loweralkyl, alkenyl, heterocyclic (alkyl), aryloxyalkyl, aryalkyl, aryl, (N-alkanoyl-N-alkyl)aminoalkyl, or alkylsulfonylamidoalkyl, and R_3 is $R_4-C(O)-R_5$ wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from alkyl, aryl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, and heterocyclic, with the proviso that one or R_{11} and R_{12} is alkyl

- 25 41. A compound selected from the group consisting of
trans-trans-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(3-(N-propyl-N-*n*-pentanesulfonylamino)propyl)pyrrolidine-3-carboxylic acid;
trans, trans-2-(4-Methoxymethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
30 *trans, trans*-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
trans, trans-2-(3,4-Dimethoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
35 *trans, trans*-2-(4-Propoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;

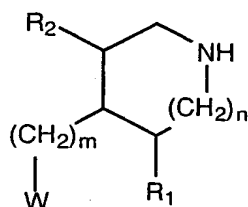
- trans,trans*-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-(((N,N-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3,4-Difluorophenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
- 5 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-*n*-hexanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(3-chloropropanesulfonyl)amino)ethyl)-pyrrolidine-3-carboxylic acid;
- 10 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(3-chloropropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(4-methylbutanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- 15 *trans,trans*-2-(4-Methoxy-3-fluorophenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(2,2,3,3,3-pentafluoropropoxyethanesulfonyl)-amino)ethyl)pyrrolidine-3-carboxylic acid;
- 20 *trans,trans*-2-(1,4-Benzodioxan-6-yl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(*n*-pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- 25 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(pentanesulfonylamino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(3-chloropropanesulfonyl)amino)-ethyl)pyrrolidine-3-carboxylic acid;
- 30 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(pentanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-((2,2,2-trifluoroethoxyethane)sulfonyl)amino)-ethyl)pyrrolidine-
- 35 3-carboxylic acid;

- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-(2-methoxyethyl)-N-(butanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid;
- 5 *trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-(2-methylpropanesulfonyl)amino)ethyl)pyrrolidine-3-carboxylic acid; and
- trans,trans*-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-isobutyl-N-(butanesulfonylamino))ethyl)pyrrolidine-3-carboxylic acid;
- 10 *trans,trans*-2-(2-Methylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 15 *trans,trans*-2-(2-(2-Tetrahydro-2H-pyran)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2,4-Trimethyl-3-pentenyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 20 *trans,trans*-2-(2,2-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(1,3-Dioxo-2-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-((N-4-heptyl-N-(2-methyl-3-fluorophenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 25 *trans,trans*-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid
- trans,trans*-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 30 *trans,trans*-2-(2-(2-Oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid
- 35 *trans,trans*-2-(2-(1,3-Dioxol-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;

- trans,trans*-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2,2-dimethylpentyl)-4-(2,3-dihydro-benzofuran-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 5 *trans,trans*-2-(2,2,-Dimethyl-2-(1,3-dioxolan-2-yl)ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(2-Methoxyphenyl)-ethyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 10 *trans,trans*-2-(2,2-Dimethyl-3-(*E*)-pentenyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(2-pyridyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 15 (*2S,3R,4S*)-2-(2-(2-oxopyrrolidin-1-yl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N-4-heptyl-N-(4-fluoro-3-methylphenyl))aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- trans,trans*-2-(2-(1-pyrazolyl)ethyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 20 *trans,trans*-2-(4-Methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((N-butyl-N-(4-dimethylaminobutyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2R,3R,4S*)-2-(3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonylamino)ethyl)-pyrrolidine-3-carboxylic acid;
- 25 (*2S,3R,4S*)-2-(2,2-Dimethylpentyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-(2,2-Dimethylpent-(*E*)-3-enyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- 30 (*2S,3R,4S*)-2-(2,2-Dimethylpent-(*E*)-3-enyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-((2-Methoxyphenoxy)-methyl)-4-(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid;
- (*2S,3R,4S*)-2-(2-(2-Methoxyphenyl)ethyl)-4(1,3-benzodioxol-5-yl)-1-(N,N-di(n-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid;
- 35 (554) *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-(pyrrolidine-3-carboxylic acid;

- (555) *trans,trans*-2-[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
 (556) *trans,trans*-2-[4-(2-methoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-((bis-(o-tolyl)methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
 5 (557) *trans,trans*-2-[4-(2-isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-(2,2-dimethyl-1-phenylpropyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
 (558) *trans,trans*-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-(3,3-dimethyl-1-phenylbutyl)-1-amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
 (559) *trans,trans*-2-[4-(2-isopropoxyethoxy)phenyl]-4-(1,3-benzodioxol-5-yl)-1-(N-
 10 ((1-(o-tolyl)-1-(o-ethylphenyl)-methyl)amino)carbonylmethyl)-pyrrolidine-3-carboxylic acid;
 (560) *trans,trans*-2-(4-(2-(2-propoxy)ethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid; and
 (561) *trans,trans*-2-(4-(2-methoxyethoxy)phenyl)-4-(1,3-benzodioxol-5-yl)-1-(N-phenyl-N-t-butylhydrazino carbonylmethyl)-pyrrolidine-3-carboxylic acid;
 15 or a pharmaceutically acceptable salt thereof.

42. A compound of the formula:



20

wherein n is 0 or 1;

m is 0 to 6;

W is (a) -C(O)₂-G where G is hydrogen or a carboxy protecting group, (b) -PO₃H₂,

25

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR₁₇ where R₁₇ is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

30

(h) tetrazolyl,

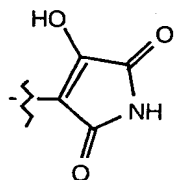
(i) hydroxy,

(j) alkoxy,

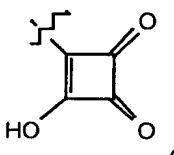
(k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

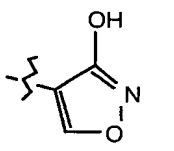
(m) $-S(O)_2NHC(O)R_{16}$.



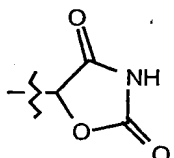
(n)



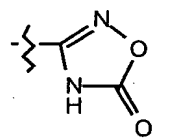
(o)



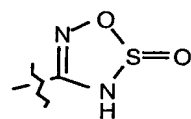
(p)



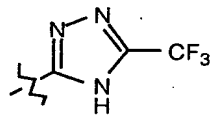
(q)



(r)

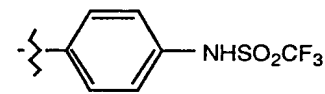


(s)



(t)

, or



(u)

; and

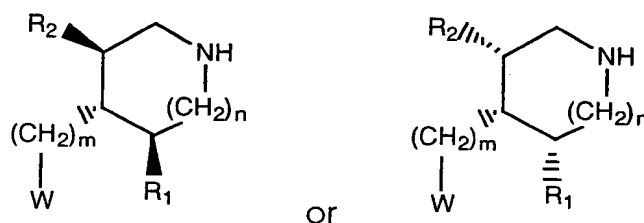
R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl,

alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen; or a salt thereof.

43. The compound of Claim 42 wherein
m is zero or 1;
W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; or
10 the substantially pure (+)- or (-)-isomer thereof.

44. The compound of Claim 42 wherein
n and m are both 0;
W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group;
15 and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-
20 methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and R_2 is substituted or
25 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or
30 the substantially pure (+)- or (-)-isomer thereof.

45. The compound according to Claim 42 of the formula:



wherein n is 0 or 1;

m is 0 to 6;

5 W is (a) $-C(O)_2-G$ where G is hydrogen or a carboxy protecting group, (b) $-PO_3H_2$,

(c) $-P(O)(OH)E$ where E is hydrogen, loweralkyl or arylalkyl,

(d) $-CN$,

(e) $-C(O)NHR_{17}$ where R_{17} is loweralkyl,

10 (f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

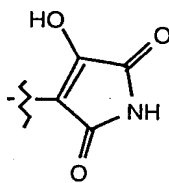
(i) hydroxy,

(j) alkoxy,

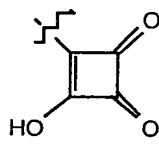
15 (k) sulfonamido,

(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or dialkylamino,

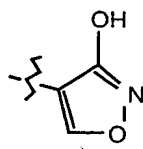
(m) $-S(O)_2NHC(O)R_{16}$.



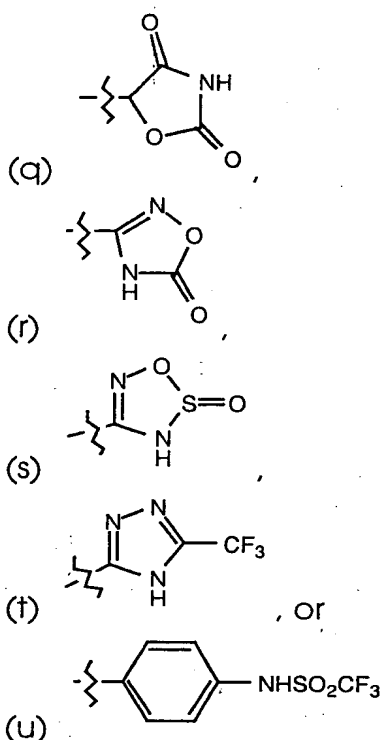
(n)



(o)



(p)



5 (u) ; and
 R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl,
 10 dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ - wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is
 15 alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;
 or a salt thereof.

46. The compound according to Claim 45 wherein
 20 m is zero or 1;
 W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

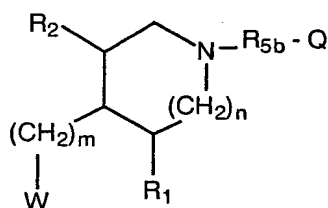
47. The compound according to Claim 45 wherein
 25 n and m are both 0;

W is -CO₂-G wherein G is hydrogen or a carboxy protecting group;
and R₁ is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl,
(vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl,
4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-
5 methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-
methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-
methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl,
1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected
from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix)
10 aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-
alkyl)aminoalkyl, or (xiii) alkysulfonylamidoalkyl, and R₂ is substituted or
unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-
benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl,
benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or
15 difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and
halogen; or
the substantially pure (+)- or (-)-isomer thereof.

48. The substantially pure compound (+)-trans,trans-2-(4-
20 Methoxyphenyl)-4-(1,3-benzodioxo-5-yl)pyrrolidine-3-carboxylic acid; or a salt
or ester thereof.

49. The substantially pure compound (2*S*,3*R*,4*S*)-2-(2,2-
Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(N,N-di(*n*-
25 butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid; or a salt or ester
thereof.

50. A compound of the formula



5 wherein n is 0 or 1;

m is 0 to 6;

R_{5b} is alkylene;

Q is a leaving group;

W is (a) -C(O)₂-G where G is hydrogen or a carboxy protecting group, (b)

10 -PO₃H₂,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR₁₇ where R₁₇ is loweralkyl,

(f) alkylaminocarbonyl,

15 (g) dialkylaminocarbonyl,

(h) tetrazolyl,

(i) hydroxy,

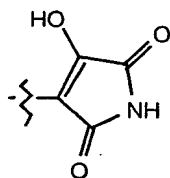
(j) alkoxy,

(k) sulfonamido,

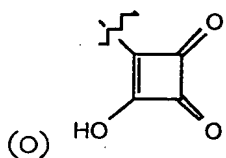
20 (l) -C(O)NHS(O)₂R₁₆ where R₁₆ is loweralkyl, haloalkyl, phenyl or

dialkylamino,

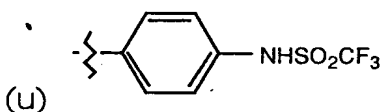
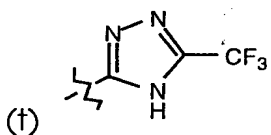
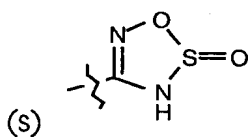
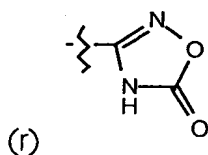
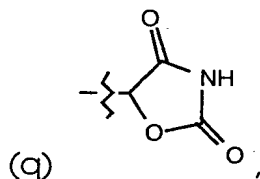
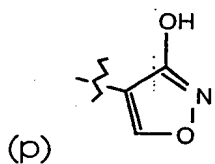
(m) -S(O)₂NHC(O)R₁₆.



(n)



(o)



; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ - wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen; or a salt thereof.

51. The compound according to Claim 50 wherein

m is zero or 1;

R_{5b} is alkylene;

Q is a leaving group; and

- 5 W is -CO₂-G wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

52. The compound according to Claim 50 wherein

n and m are both 0;

- 10 R_{5b} is alkylene;

Q is a leaving group;

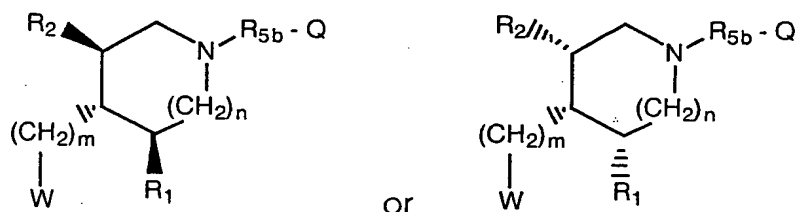
W is -CO₂-G wherein G is hydrogen or a carboxy protecting group;

and R₁ is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl,

- 15 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy and R₂ is
- 20 substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and
- 25 halogen, (ix) aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl; or the substantially pure (+)- or (-)-isomer thereof.

53. The compound according to Claim 50 of the formula

30



wherein n is 0 or 1;

m is 0 to 6;

R_{5b} is alkylene;

Q is a leaving group;

W is (a) -C(O)₂-G where G is hydrogen or a carboxy protecting group, (b)

5 -PO₃H₂,

(c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR₁₇ where R₁₇ is loweralkyl,

(f) alkylaminocarbonyl,

10 (g) dialkylaminocarbonyl,

(h) tetrazolyl,

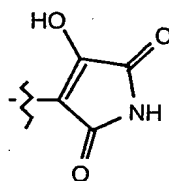
(i) hydroxy,

(j) alkoxy,

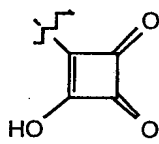
(k) sulfonamido,

15 (l) -C(O)NHS(O)₂R₁₆ where R₁₆ is loweralkyl, haloalkyl, phenyl or dialkylamino,

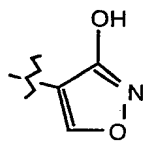
(m) -S(O)₂NHC(O)R₁₆,



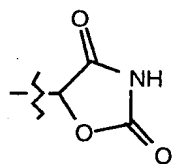
(n)



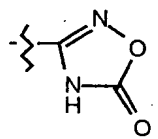
(o)



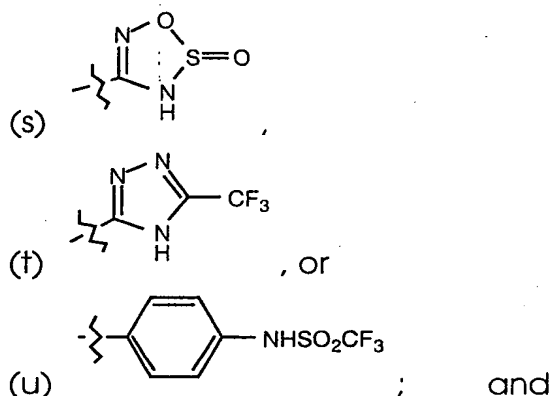
20 (p)



(q)



(r)



R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl,

- 5 alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl,
- 10 aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen; or a salt thereof.

15

54. The compound according to Claim 53 wherein m is zero or 1; R_{5b} is alkylene; Q is a leaving group; W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

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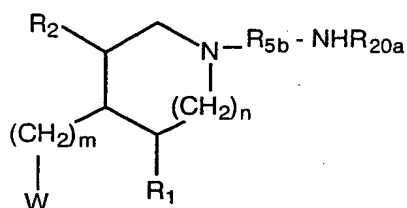
55. The compound according to Claim 53 wherein n and m are both 0; R_{5b} is alkylene; Q is a leaving group; W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl,

25 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected

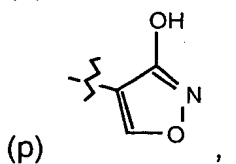
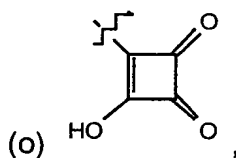
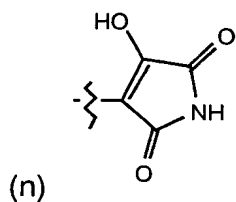
30 from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy and R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl,

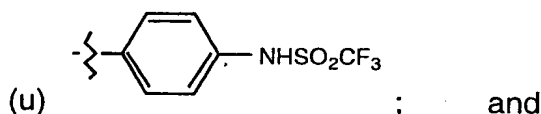
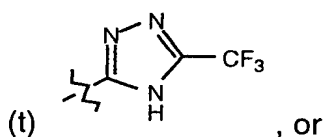
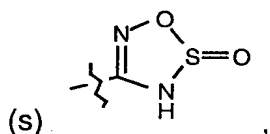
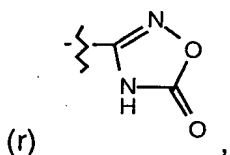
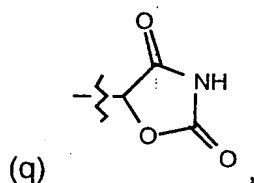
1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen, (ix) aryalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-
5 N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl; or the substantially pure (+)- or (-)-isomer thereof.

56. A compound of the formula



- 5 wherein n is 0 or 1; m is 0 to 6; R_{5b} is alkylene;
R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl,
cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;
W is (a) -C(O)₂-G where G is hydrogen or a carboxy protecting group, (b)
-PO₃H₂,
10 (c) -P(O)(OH)E where E is hydrogen, loweralkyl or arylalkyl,
(d) -CN,
(e) -C(O)NHR₁₇ where R₁₇ is loweralkyl,
(f) alkylaminocarbonyl,
(g) dialkylaminocarbonyl,
15 (h) tetrazolyl,
(i) hydroxy,
(j) alkoxy,
(k) sulfonamido,
(l) -C(O)NHS(O)₂R₁₆ where R₁₆ is loweralkyl, haloalkyl, phenyl or
dialkylamino,
20 (m) -S(O)₂NHC(O)R₁₆,





R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen; or a salt thereof.

57. The compound according to Claim 56 wherein

m is zero or 1;

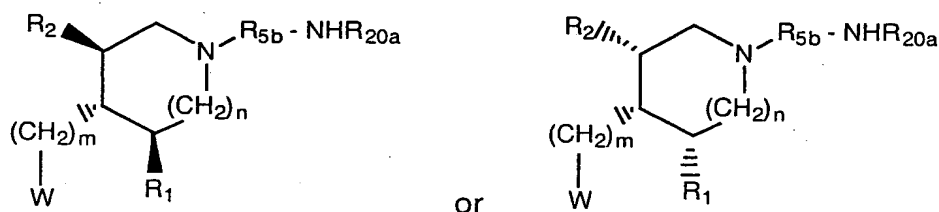
R_{5b} is alkylene;

R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl; and

W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

58. The compound according to Claim 56 wherein
 n and m are both 0;
 R_{5b} is alkylene;
 R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl,
 5 cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;
 W is $-\text{CO}_2\text{-G}$ wherein G is hydrogen or a carboxy protecting group;
 and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi)
 pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-
 fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-
 10 trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-
 4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-t-
 butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein
 the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and
 carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-
 15 N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and R_2 is substituted or
 unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-
 methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl,
 dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected
 from loweralkyl, alkoxy and halogen; or
 20 the substantially pure (+)- or (-)-isomer thereof.

59. The compound according to Claim 56 of the formula



- 25 wherein n is 0 or 1; m is 0 to 6; R_{5b} is alkylene; R_{20a} is hydrogen, loweralkyl, alkenyl,
 haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl;
 W is (a) $-\text{C}(\text{O})_2\text{-G}$ where G is hydrogen or a carboxy protecting group, (b)
 $-\text{PO}_3\text{H}_2$,
 30 (c) $-\text{P}(\text{O})(\text{OH})\text{E}$ where E is hydrogen, loweralkyl or arylalkyl,
 (d) $-\text{CN}$,
 (e) $-\text{C}(\text{O})\text{NHR}_{17}$ where R_{17} is loweralkyl,
 (f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

(h) tetrazolyl,

(i) hydroxy,

(j) alkoxy,

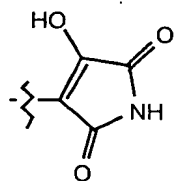
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(k) sulfonamido,

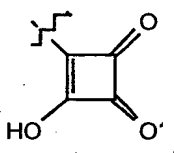
(l) $-C(O)NHS(O)_2R_{16}$ where R_{16} is loweralkyl, haloalkyl, phenyl or

dialkylamino,

(m) $-S(O)_2NHC(O)R_{16}$.

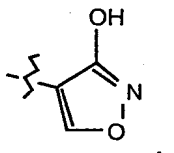


(n)

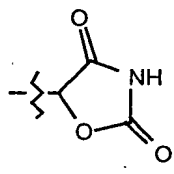


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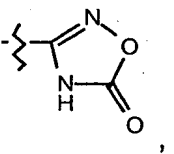
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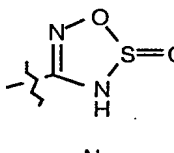
(p)



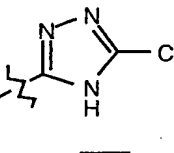
(q)



(r)

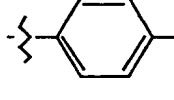


(s)



(t)

15



(u)

, or

; and

R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen; or a salt thereof.

60. The compound according to Claim 59 wherein m is zero or 1; R_{5b} is alkylene; R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl; and W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; or the substantially pure (+)- or (-)-isomer thereof.

61. The compound according to Claim 58 wherein n and m are both 0; R_{5b} is alkylene; R_{20a} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl; W is $-CO_2-G$ wherein G is hydrogen or a carboxy protecting group; and R_1 is (i) loweralkyl, (ii) alkenyl, (iii) alkoxyalkyl, (iv) cycloalkyl, (v) phenyl, (vi) pyridyl, (vii) furanyl or (viii) substituted or unsubstituted 4-methoxyphenyl, 4-fluorophenyl, 3-fluorophenyl, 4-ethoxyphenyl, 4-ethylphenyl, 4-methylphenyl, 4-trifluoromethylphenyl, 4-pentafluoroethylphenyl, 3-fluoro-4-methoxyphenyl, 3-fluoro-4-ethoxyphenyl, 2-fluorophenyl, 4-methoxymethoxyphenyl, 4-hydroxyphenyl, 4-*t*-butylphenyl, 1,3-benzodioxolyl, 1,4-benzodioxanyl or dihydrobenzofuranyl wherein the substituent is selected from loweralkyl, haloalkyl, alkoxy, alkoxyalkoxy and carboxyalkoxy, (ix) arylalkyl, (x) aryloxyalkyl, (xi) heterocyclic (alkyl), (xii) (N-alkanoyl-N-alkyl)aminoalkyl, or (xiii) alkylsulfonylamidoalkyl, and R_2 is substituted or unsubstituted 1,3-benzodioxolyl, 7-methoxy-1,3-benzodioxolyl, 1,4-benzodioxanyl, 8-methoxy-1,4-benzodioxanyl, dihydrobenzofuranyl, benzofuranyl, 4-methoxyphenyl, dimethoxyphenyl, fluorophenyl or difluorophenyl wherein the substituent is selected from loweralkyl, alkoxy and halogen; or the substantially pure (+)- or (-)-isomer thereof.

62. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of the compound of Claim 1 and a pharmaceutically acceptable carrier.

63. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of the compound of Claim 21 and a pharmaceutically acceptable carrier.

64. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid and a pharmaceutically acceptable carrier.

65. A pharmaceutical composition for antagonizing the action of endothelin comprising a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(*N*-propyl-*N*-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid and a pharmaceutically acceptable carrier.

66. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

67. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21.

68. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

69. A method for antagonizing the action of endothelin comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(*N*-propyl-*N*-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

70. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,
5 pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

71. A method for treating coronary angina, cerebral vasospasm, acute and
10 chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-reperfusion injury, raynaud's disease and migraine comprising
15 administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 1.

72. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,
20 pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21.

73. A method for treating hypertension, congestive heart failure, restenosis
25 following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-
30 carboxylic acid.

74. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina,
35 pulmonary hypertension, migraine, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-

benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

5 75. A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders,
10 ischemia-reperfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of claim 21.

15 76. A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-reperfusion injury, raynaud's disease and migraine comprising
20 administering to a mammal in need of such treatment a therapeutically effective amount of a compound of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N,N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid.

25 77. A method for treating coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders,
30 ischemia-reperfusion injury, raynaud's disease and migraine comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of (2*S*,3*R*,4*S*)-2-3-Fluoro-4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(2-(N-propyl-N-pentanesulfonyl)ethyl)-pyrrolidine-3-carboxylic acid.

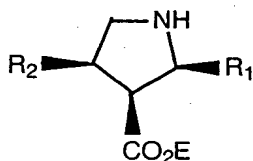
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78. A method for treating treating hypertension, congestive heart failure, restenosis following arterial injury, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1 in combination with one or more cardiovascular agents.

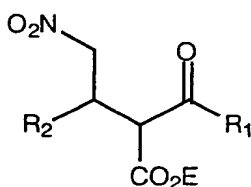
79. A method for treating treating hypertension, congestive heart failure, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 21 in combination with one or more cardiovascular agents.

80. A method for treating treating hypertension, congestive heart failure, cerebral or myocardial ischemia or atherosclerosis comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of (2*S*,3*R*,4*S*)-2-(2,2-Dimethylpentyl)-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(*N*,*N*-di(*n*-butyl)aminocarbonylmethyl)-pyrrolidine-3-carboxylic acid in combination with one or more cardiovascular agents.

81. A process for the preparation of a compound of the formula:



wherein E is a carboxy-protecting group and R₁ and R₂ are independently selected from loweralkyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl; or a salt thereof, comprising a) catalytic hydrogenation of a compound of the formula:



wherein E, R₁ and R₂ are defined as above and b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids.

5

82. The process of Claim 71 wherein E is loweralkyl, R₁ is aryl and R₂ is heterocyclic.

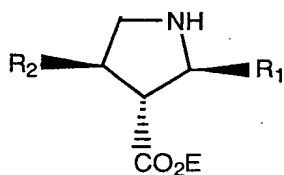
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83. The process of Claim 71 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

84. The process of Claim 71 wherein E is loweralkyl, R₁ is 4-methoxyphenyl and R₂ is 1,3-benzodioxol-5-yl.

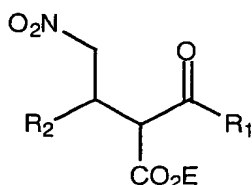
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85. A process for the preparation of a compound of the formula:



wherein E is a carboxy-protecting group and R₁ and R₂ are independently selected from loweralkyl, alkoxyalkyl, alkoxyalkylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl; or a salt thereof, comprising

a) catalytic hydrogenation of a compound of the formula:



wherein E, R₁ and R₂ are defined as above,

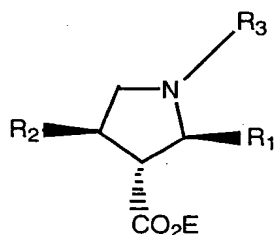
- b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids, and
 5 c) epimerization of the product of step b) with a base.

86. The process of Claim 75 wherein E is loweralkyl, R₁ is aryl and R₂ is heterocyclic.

10 87. The process of Claim 75 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

88. The process of Claim 75 wherein E is loweralkyl, R₁ is
 15 4-methoxyphenyl and R₂ is 1,3-benzodioxol-5-yl.

89. A process for the preparation of a compound of the formula:



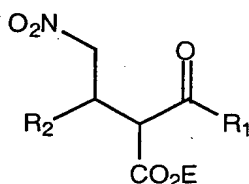
20 wherein E is a carboxy-protecting group, R₁ and R₂ are independently selected from loweralkyl, alkoxyalkyl, alkoxyalkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl,
 25 aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic and (heterocyclic)alkyl and R₃ is R₄-C(O)-R₅-

wherein R_5 is alkylene and R_4 is $(R_{11})(R_{12})N$ - wherein R_{11} and R_{12} are independently selected from

- (1) loweralkyl,
- (2) haloalkyl,
- 5 (3) alkoxyalkyl,
- (4) haloalkoxyalkyl,
- (5) alkenyl,
- (6) alkynyl,
- (7) cycloalkyl,
- 10 (8) cycloalkylalkyl,
- (9) aryl,
- (10) heterocyclic,
- (11) arylalkyl and
- (12) (heterocyclic)alkyl;
- 15 (13) hydroxyalkyl,
- (14) alkoxy,
- (15) aminoalkyl, and
- (16) trialkylaminoalkyl,

or a salt thereof, comprising

- 20 a) catalytic hydrogenation of a compound of the formula:



wherein E, R_1 and R_2 are defined as above,

- 25 b) catalytic hydrogenation of the product of step a) in the presence of an acid or a mixture of acids,
- c) epimerization of the product of step b) with a base and
- d) alkylation of the product of step c) with a compound of the formula R_3-X wherein X is a leaving group and R_3 is defined as above.

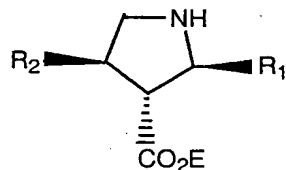
30

90. The process of Claim 79 wherein E is loweralkyl, R_1 is aryl, R_2 is heterocyclic and R_3 is $-CH_2C(O)NR_{11}R_{12}$ wherein R_{11} and R_{12} are independently selected from the group consisting of loweralkyl.

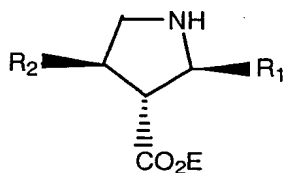
91. The process of Claim 79 wherein the hydrogenation catalyst is Raney nickel and the acid is a mixture of acetic acid and trifluoroacetic acid.

5 92. The process of Claim 79 wherein E is loweralkyl, R_1 is 4-methoxyphenyl, R_2 is 1,3-benzodioxol-5-yl, R_3 is $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{n-Bu})_2$ and X is a halogen or sulfonate leaving group.

10 93. A process for the preparation of the substantially pure (+)-trans,trans optical isomer of the compound of the formula:

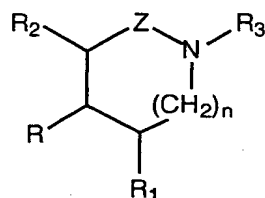


15 wherein E is loweralkyl, R_1 is 4-methoxyphenyl and R_2 is 1,3-benzodioxol-5-yl, or a salt thereof, comprising reacting a mixture of the (+) and (-) enantiomers of the compound of the formula:



20 wherein E is loweralkyl, R_1 is 4-methoxyphenyl and R_2 is 1,3-benzodioxol-5-yl with S-(+)- mandelic acid and separating the mandelate salt of the (+)-trans,trans optical isomer.

25 94. A compound of the formula:



wherein

Z is -C(R₁₈)(R₁₉)- or -C(O)- wherein R₁₈ and R₁₉ are independently selected from

5 hydrogen and loweralkyl;

n is 0 or 1;

R is -(CH₂)_m-W wherein m is an integer from 0 to 6 and W is

(a) -C(O)₂-G wherein G is hydrogen or a carboxy protecting group,

(b) -PO₃H₂,

10 (c) -P(O)(OH)E wherein E is hydrogen, loweralkyl or arylalkyl,

(d) -CN,

(e) -C(O)NHR₁₇ wherein R₁₇ is loweralkyl,

(f) alkylaminocarbonyl,

(g) dialkylaminocarbonyl,

15 (h) tetrazolyl,

(i) hydroxy,

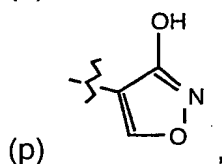
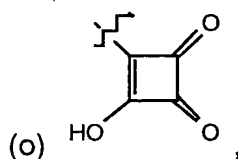
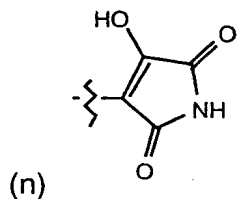
(j) alkoxy,

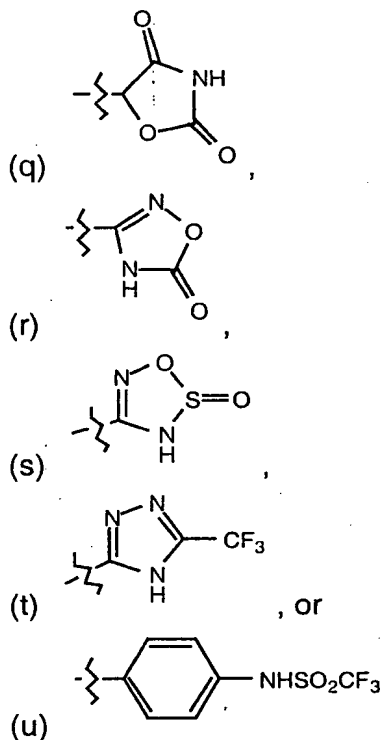
(k) sulfonamido,

(l) -C(O)NHS(O)₂R₁₆ wherein R₁₆ is loweralkyl, haloalkyl, aryl or

20 dialkylamino,

(m) -S(O)₂NHC(O)R₁₆ wherein R₁₆ is defined as above,





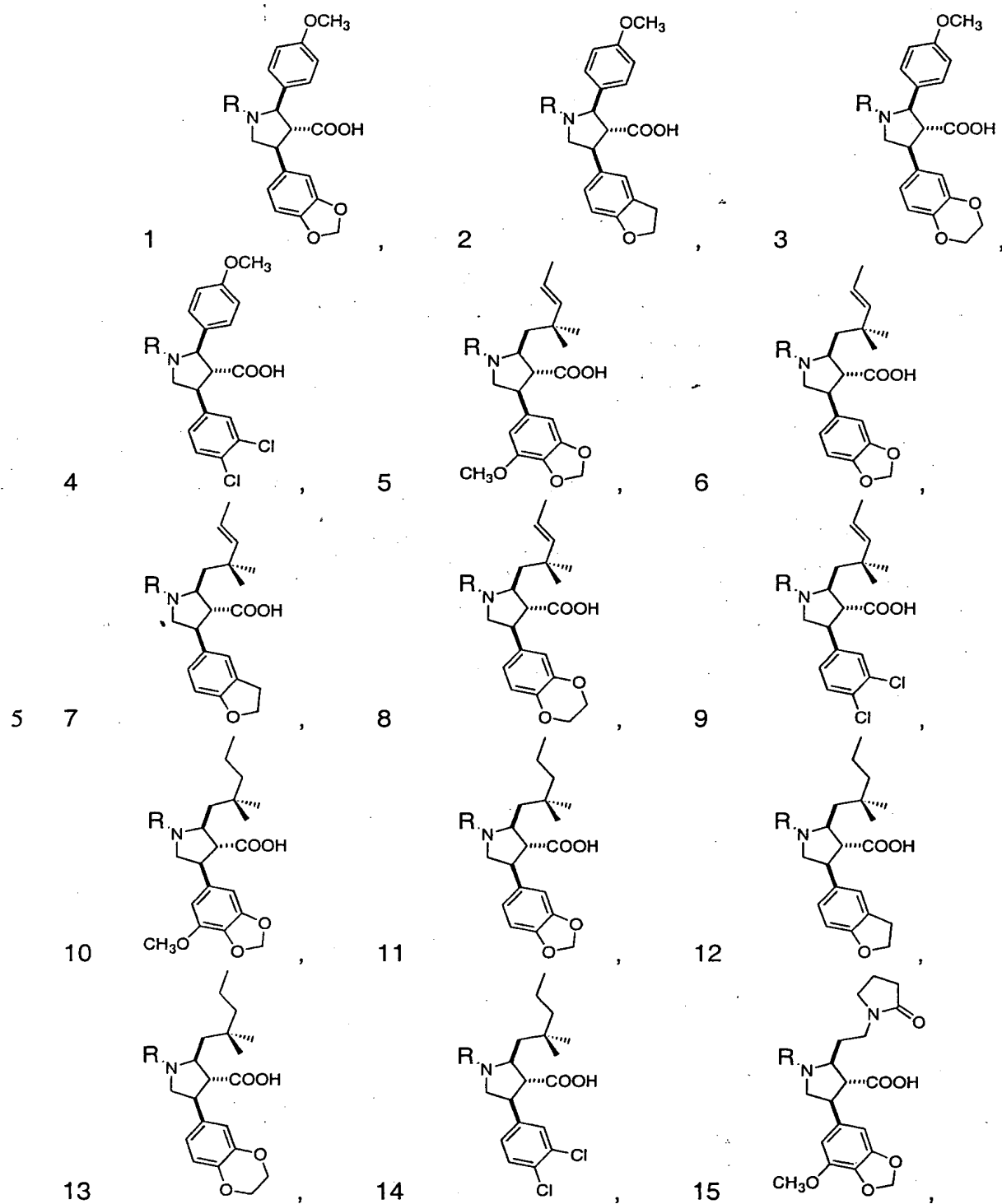
5 (u) ;
 R_1 and R_2 are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl and $(R_{aa})(R_{bb})N-R_{cc}$ - wherein R_{aa} is aryl or arylalkyl, R_{bb} is hydrogen or alkanoyl and R_{cc} is alkylene, with the proviso that one or both of R_1 and R_2 is other than hydrogen;

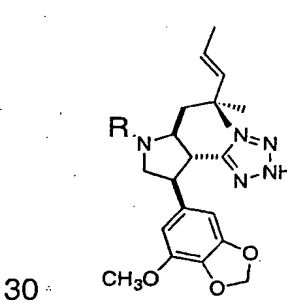
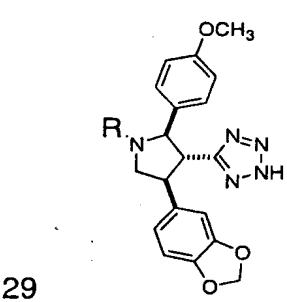
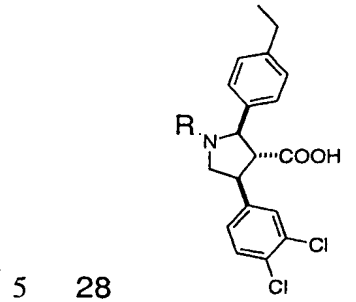
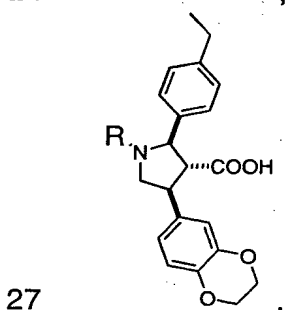
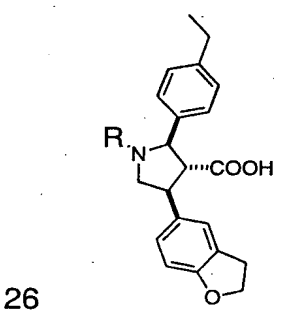
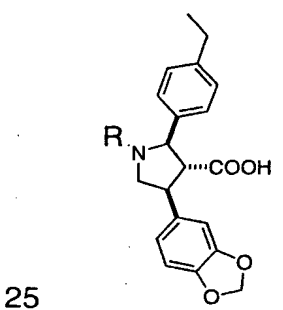
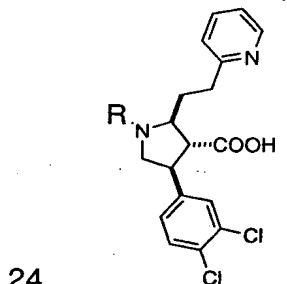
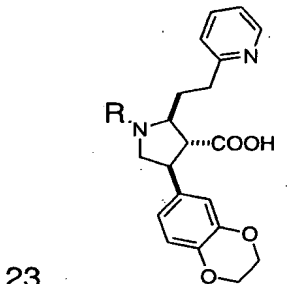
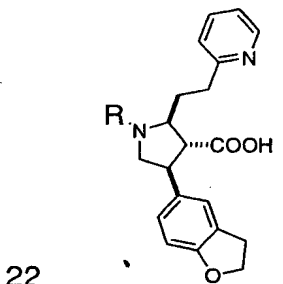
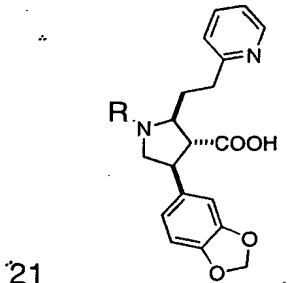
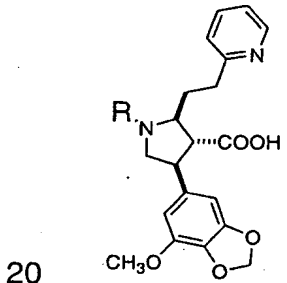
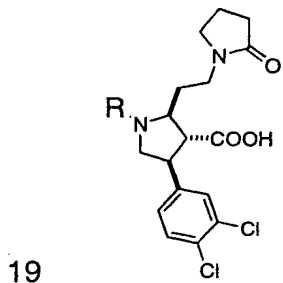
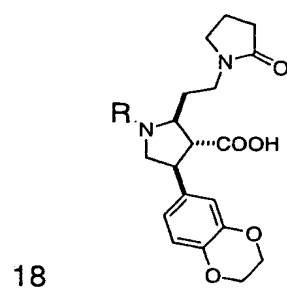
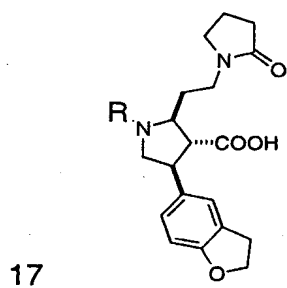
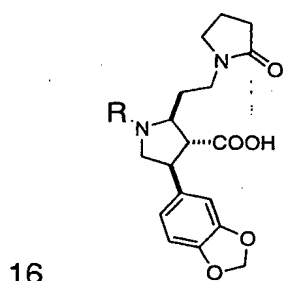
R_3 is (a) $R_4-C(O)-R_5-$, $R_4-C(O)-R_5-N(R_6)-$,
 wherein R_5 is (i) a covalent bond, (ii) alkylene, (iii) alkenylene, (iv) $-N(R_{20})-R_8-$ or $-R_{8a}-N(R_{20})-R_8-$
 20 wherein R_8 and R_{8a} are independently selected from the group consisting of alkylene and alkenylene and R_{20} is hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl or cycloalkylalkyl or (v) $-O-R_9-$ or $-R_{9a}-O-R_9-$ wherein R_9 and R_{9a} are independently selected from alkylene;

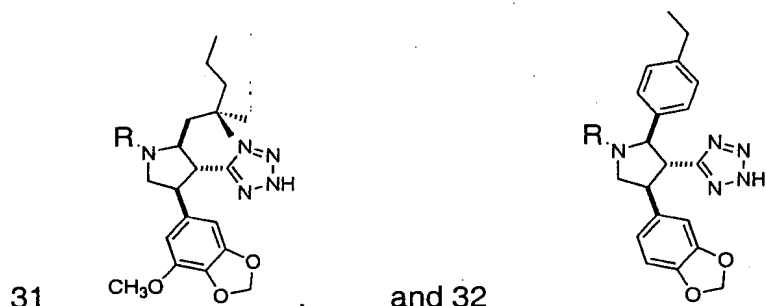
R_4 and R_6 are $(R_{11})(R_{12})N-$ wherein R_{11} and R_{12} are independently selected from
 25 (1) hydrogen,

- 5 (2) loweralkyl,
(3) haloalkyl,
(4) alkoxyalkyl,
(5) haloalkoxyalkyl,
(6) alkenyl,
(7) alkynyl,
(8) cycloalkyl,
(9) cycloalkylalkyl,
10 (10) aryl,
(11) heterocyclic,
(12) arylalkyl,
(13) (heterocyclic)alkyl,
(14) hydroxyalkyl,
(15) alkoxy,
(16) aminoalkyl,
(17) trialkylaminoalkyl,
(18) alkylaminoalkyl,
(19) dialkylaminoalkyl,
20 (25) carboxyalkyl,
(26) (cycloalkyl)aminoalkyl,
(27) (cycloalkyl)alkylaminoalkyl,
(28) (heterocyclic)aminoalkyl, and
(29) (heterocyclic)aminoalkyl, with the proviso that at least one of
25 R_{11} and R_{12} is selected from heterocyclic, aminoalkyl,
alkylaminoalkyl, dialkylaminoalkyl, trialkylaminoalkyl,
alkylaminoalkyl, dialkylaminoalkyl, carboxyalkyl,
(cycloalkyl)aminoalkyl, (cycloalkyl)alkylaminoalkyl,
(heterocyclic)aminoalkyl, and (heterocyclic)alkylaminoalkyl;
or a pharmaceutically acceptable salt thereof.
30

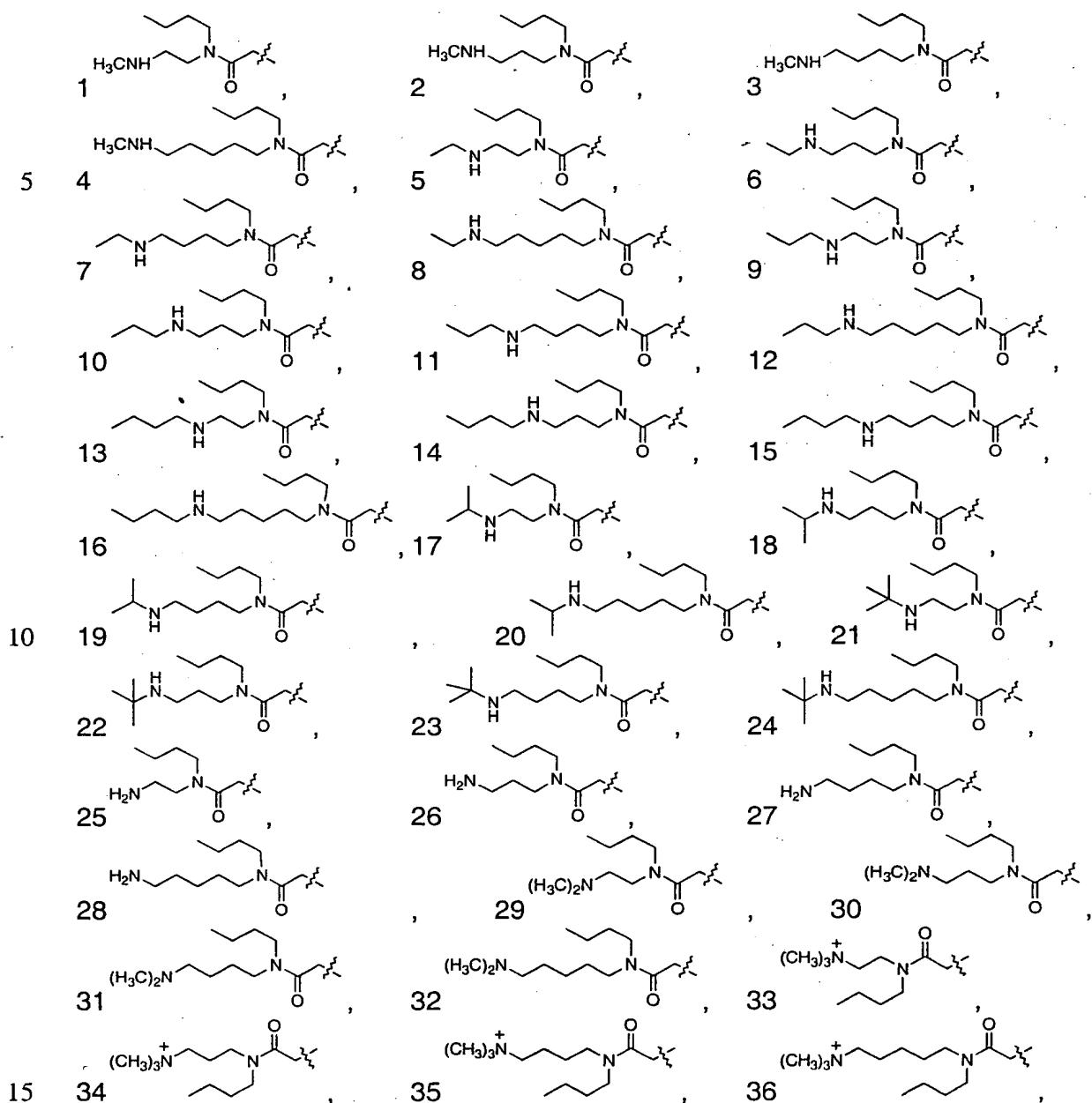
95. A compound selected from the group consisting of:

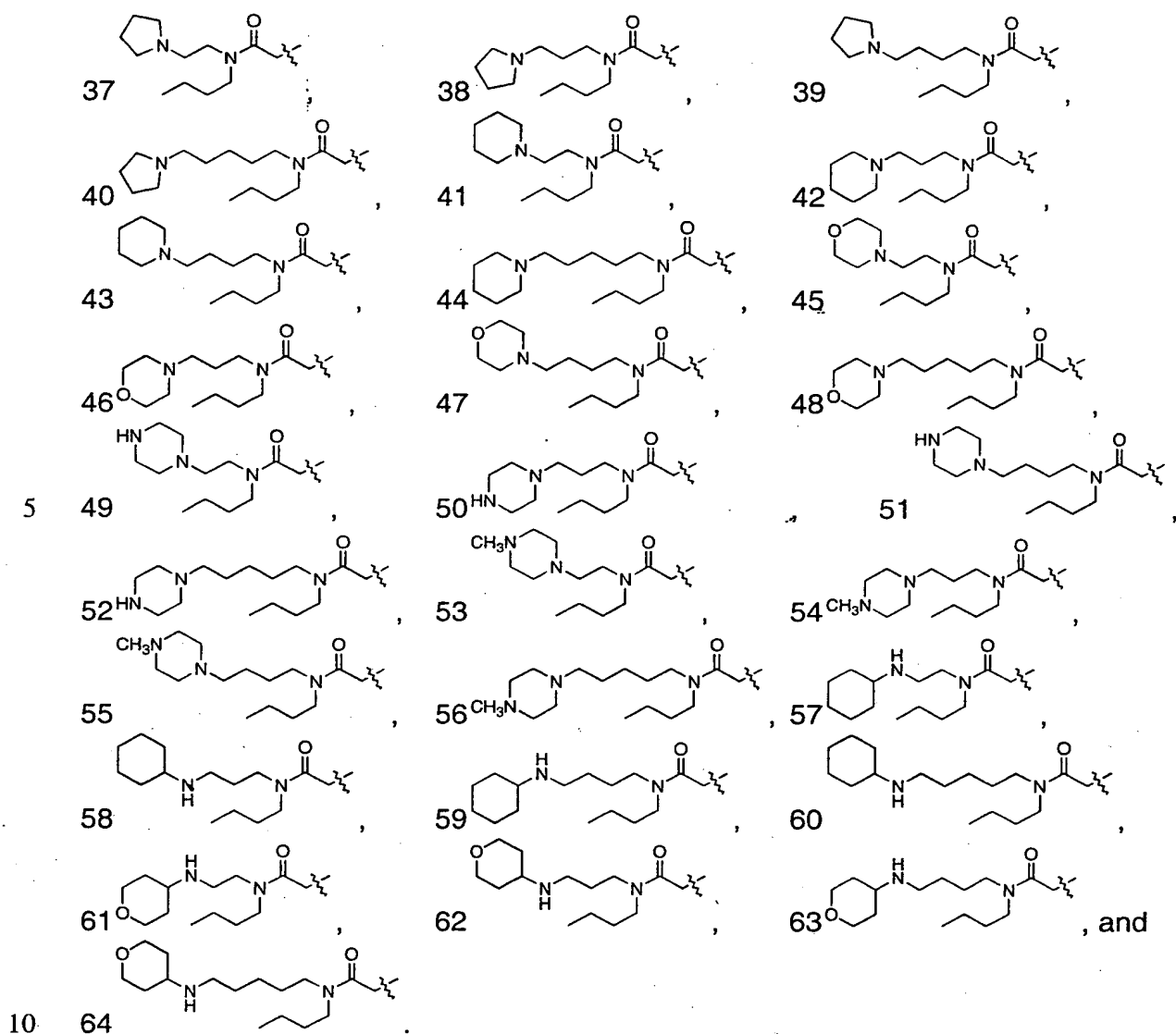






wherein R is selected from the group consisting of:





96. A method for treating hypertension, congestive heart failure, restenosis following arterial injury, renal failure, cancer, colitis, reperfusion injury, angina, pulmonary hypertension, migraine, cerebral or myocardial ischemia, atherosclerosis, coronary angina, cerebral vasospasm, acute and chronic renal failure, gastric ulceration, cyclosporin-induced nephrotoxicity, endotoxin-induced toxicity, asthma, LPL-related lipoprotein disorders, proliferative diseases, acute or chronic pulmonary hypertension, platelet aggregation, thrombosis, IL-2 mediated cardiotoxicity, nociception, colitis, vascular permeability disorders, ischemia-reperfusion injury, Raynaud's disease, prostatic hyperplasia, and migraine comprising a therapeutically effective amount of a compound of claim 94, wherein said compound has an

attached charged functionality which reduces the degree of plasma protein binding of the compound.

5 97. A method of improving the *in vivo* activity of compounds by reducing the amount of compound bound to protein by attaching a charged functionality to the compound.

 98. A method of claim 97 wherein the charged functionality carries a positive charge at physiological pH.

10

 99. A method for inhibiting bone metastases and metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

15

 100. The method of Claim 99 wherein the bone metastases are osteoblastic.

 101. The method of Claim 100 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

20

 102. The method of Claim 101 wherein the primary cancer is prostate cancer and the patient is male.

25 103. The method of Claim 99 which additionally comprises co-administration of an anticancer drug.

 104. The method of Claim 103 wherein the anticancer drug agent is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

30

 105. The method of Claim 99 which additionally comprises the administration of radiation therapy.

35

 106. The method of Claim 99 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

107. The method of Claim 106 wherein the therapeutic agent is a bisphosphonate.

5 108. The method of Claim 99 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

10 109. A method for the inhibition of bone loss in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

110. The method of Claim 109 wherein the patient has cancer.

15 111. The method of Claim 109 wherein the cancer is prostate cancer and the patient is male.

112. The method of Claim 109 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

20 113. The method of Claim 112 wherein the therapeutic agent is a bisphosphonate.

25 114. A method for the reduction of cancer-related pain in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

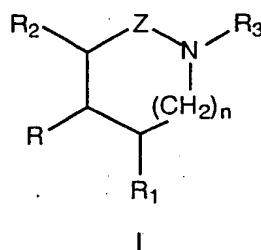
115. The method of Claim 114 wherein the cancer is prostate cancer and the patient is male.

30 116. The method of Claim 114 which additionally comprises the administration of an anticancer drug.

35 117. The method of Claim 116 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

118. The method of Claim 115 which additionally comprises the administration of radiation therapy.

119. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



wherein

10 R is $-(CH_2)_m-W$;

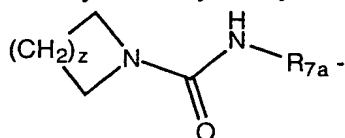
Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxyalkonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}$,

20 with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)₂-R₇-, R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-

25 R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



30 R₅ is selected from a covalent bond, alkylene, alkenylene, $-N(R_{20})-R_8-$, $-R_{8a}-N(R_{20})-R_8-$, $-O-R_9-$, and

-R_{9a}-O-R₉-;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-

5 R₁₀-;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

10 R₁₁ and R₁₂ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

15 R₁₅ is selected from amino, alkylamino and dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl;

20 R₂₀ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R₂₂ is selected from a carboxy protecting group and heterocyclic;

R₂₃ is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

25 R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

30 R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

35 R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{CC} is alkylene;

m is 0-6;

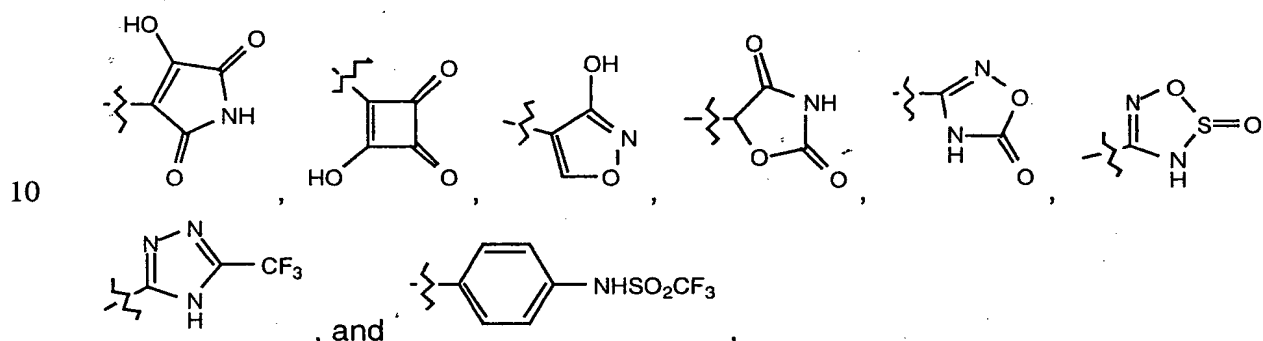
n is 0 or 1;

z is 0-5;

5 E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from $-C(O)_2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$,
 $-CN$, $-C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy,
 alkoxy, sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,



or a pharmaceutically acceptable salt thereof.

15 120. The method of Claim 119 wherein the bone metastases are osteoblastic.

121. The method of Claim 120 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

20 122. The method of Claim 121 wherein the primary cancer is prostate cancer and the patient is male.

25 123. The method of Claim 119 which additionally comprises the administration of an anticancer drug.

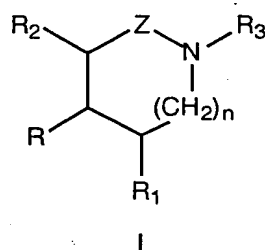
30 124. The method of Claim 123 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

125. The method of Claim 119 which additionally comprises the administration of radiation therapy.

126. The method of Claim 119 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

127. The method of Claim 126 wherein the therapeutic agent is a bisphosphonate.

128. A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



wherein,

R is $-(CH_2)_m-W$;

Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

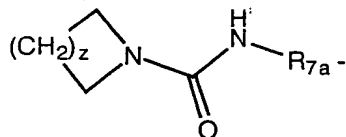
R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)₂-R₇-, R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-;

R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl,

alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



5 R₅ is selected from a covalent bond, alkylene, alkenylene, -N(R₂₀)-R₈-, -R_{8a}-, N(R₂₀)-R₈-, -O-R₉-, and -R_{9a}-O-R₉-;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

10 R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀-;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

15 R₁₁ and R₁₂ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

20 R₁₅ is selected from amino, alkylamino and dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl;

25 R₂₀ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R₂₂ is selected from a carboxy protecting group and heterocyclic;

R₂₃ is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

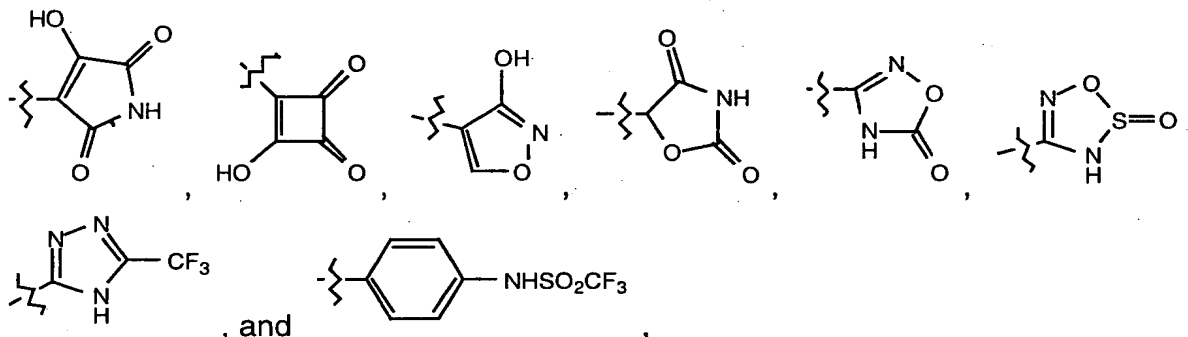
30 R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

35 R₂₇ is selected from alkylene and alkenylene;

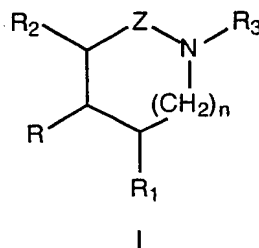
- R_{5a} is selected from alkylene and alkenylene;
 R_{7a} is alkylene;
 R_{8a} is selected from alkylene and alkenylene;
 R_{9a} is alkylene;
 5 R_{10a} is selected from alkylene and alkenylene;
 R_{aa} is selected from aryl and arylalkyl;
 R_{bb} is selected from hydrogen and alkanoyl;
 R_{cc} is alkylene;
 m is 0-6;
 10 n is 0 or 1;
 z is 0-5;
 E is selected from hydrogen, loweralkyl and arylalkyl;
 G is selected from hydrogen and a carboxy protecting group; and
 W is selected from -C(O)₂-G; -PO₃H₂; -P(O)(OH)(E),
 15 -CN, -C(O)NHR₁₇, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy,
 alkoxy, sulfonamido, -C(O)NHS(O)₂R₁₆, -S(O)₂NHC(O)R₁₆,



or a pharmaceutically acceptable salt thereof.

- 20 129. The method of Claim 128 wherein the cancer is prostate cancer and the patient is male.
 130. The method of Claim 128 which additionally comprises the
 25 administration of at least one therapeutic agent which impedes net bone loss.
 131. The method of Claim 130 wherein the therapeutic agent is a bisphosphonate.

132. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



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wherein

R is $-(CH_2)_m-W$;

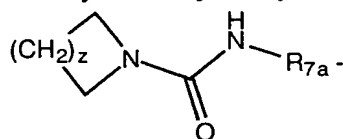
Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

10 R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (N-alkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and (R_{aa})(R_{bb})N-R_{cc}-;

15 with the proviso that one or both of R₁ and R₂ is other than hydrogen;

20 R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)₂-R₇- R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-

25 R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R₅ is selected from a covalent bond, alkylene, alkenylene, $-N(R_{20})-R_8-$, $-R_{8a}-N(R_{20})-R_8-$, $-O-R_9-$, and $-R_{9a}-O-R_9-$;

30 R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R7 is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀-;

R8 is selected from alkylene and alkenylene;

R9 is alkylene;

5 R10 is selected from alkylene and alkenylene;

R11 and R12 are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

10 R13 is selected from amino, alkylamino and dialkylamino;

R14 is selected from aryl and R15-C(O)-;

R15 is selected from amino, alkylamino and dialkylamino;

R16 is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R17 is loweralkyl;

15 R18 and R19 are independently selected from hydrogen and loweralkyl;

R20 is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R21 is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

20 R22 is selected from a carboxy protecting group and heterocyclic;

R23 is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

R24 is selected from hydrogen and loweralkyl;

R25 is alkylene;

25 R26 is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

R27 is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

30 R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

35 R_{cc} is alkylene;

m is 0-6;

n is 0 or 1;

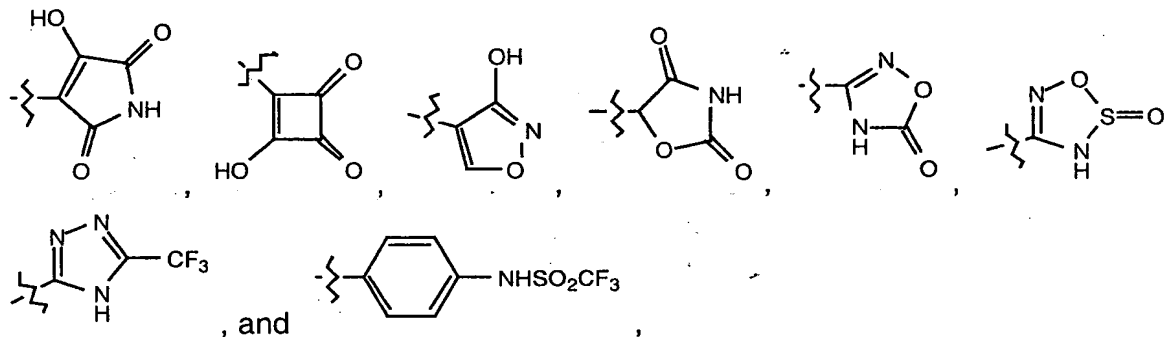
z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from $-C(O)_2G$, $-PO_3H_2$, $-P(O)(OH)(E)$,

- 5 $-CN$, $-C(O)NHR_{17}$, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, $-C(O)NHS(O)_2R_{16}$, $-S(O)_2NHC(O)R_{16}$,



or a pharmaceutically acceptable salt thereof.

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133. The method of Claim 132 wherein the cancer is prostate cancer and the patient is male.

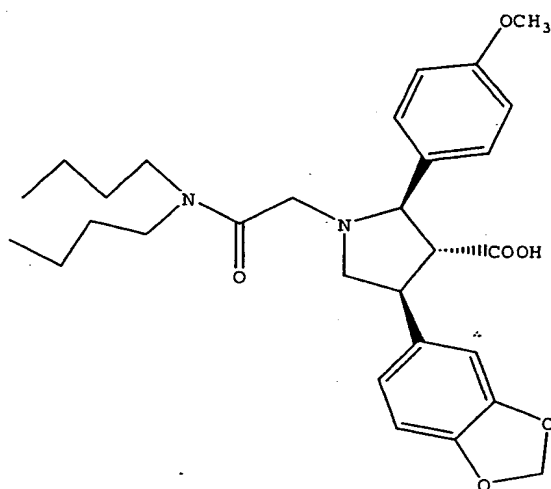
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134. The method of Claim 132 which additionally comprises the administration of an anticancer drug.

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135. The method of Claim 134 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

136. A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula IIIa



IIIa.

137. The method of Claim 136 wherein the bone metastases are osteoblastic.

138. The method of Claim 137 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

139. The method of Claim 138 wherein the primary cancer is prostate cancer and the patient is male.

140. The method of Claim 138 which additionally comprises the administration of an anticancer drug.

141. The method of Claim 140 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

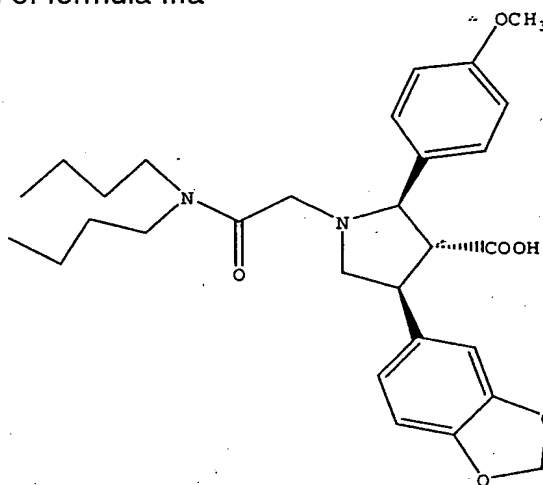
142. The method of Claim 138 which additionally comprises the administration of radiation therapy.

143. The method of Claim 138 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

144. The method of Claim 143 wherein the agent is a bisphosphonate.

145. The method of Claim 138 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

5 146. A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula IIIa



IIIa.

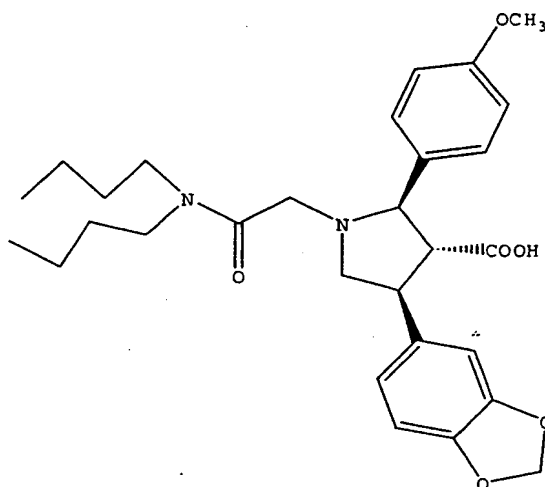
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147. The method of Claim 146 wherein the cancer is prostate cancer and the patient is male.

15 148. The method of Claim 146 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

149. The method of Claim 148 wherein therapeutic agent is a bisphosphonate.

20 150. A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula IIIa



IIIa.

5 151. The method of Claim 150 wherein the cancer is prostate cancer and the patient is male.

152. The method of Claim 150 which additionally comprises the administration of an anticancer drug.

10 153. The method of Claim 152 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

15 154. A method for preventing new bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

20 155. A method for inhibiting metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

25 156. A method for inhibiting bone turnover in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

157. A compound according to Claim 1 of formula (I) wherein n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen; R₁ is aryl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; R₃ is R₄-C(O)-R₅- wherein R₅ is methylene and R₄ is selected from (R₁₁)(R₁₂)N- and (R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and R₁₂ is hydrogen and the other is selected from arylalkyl and diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is aryl.

158. A compound according to Claim 1 of formula (I) wherein n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen; R₁ is phenyl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; R₃ is R₄-C(O)-R₅- wherein R₅ is methylene and R₄ is selected from (R₁₁)(R₁₂)N- and (R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and R₁₂ is hydrogen and the other is selected from phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl.

159. A compound according to Claim 1 of formula (II) wherein n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen; R₁ is aryl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; R₃ is R₄-C(O)-R₅- wherein R₅ is methylene and R₄ is selected from (R₁₁)(R₁₂)N- and (R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and R₁₂ is hydrogen and the other is selected from arylalkyl and diarylalkyl wherein each aryl group of the diarylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is aryl.

160. A compound according to Claim 1 of formula (II) wherein n is zero; Z is -CH₂- wherein R₁₈ and R₁₉ are hydrogen; R is C(O)-G wherein G is hydrogen; R₁ is phenyl substituted with one substituent selected from methoxy, methoxyethoxy, and isopropoxyethoxy; R₂ is 1,3-benzodiox-5-yl; R₃ is R₄-C(O)-R₅- wherein R₅ is methylene and R₄ is selected from (R₁₁)(R₁₂)N- and (R_{11a})(R_{12a})N-N(H)-; one of R₁₁ and R₁₂ is hydrogen and the other is selected from phenylalkyl and diphenylalkyl wherein each phenyl group of the diphenylalkyl is substituted with methyl or ethyl; and one of R_{11a} or R_{12a} is alkyl and the other is phenyl.